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Clues Potentially Distinguishing Lytic Lesions of Multiple Myeloma From Those of Metastatic Carcinoma

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ABSTRACT This study was conducted to determine whether individual bony lesions are specific for recognizing multiple myeloma and thereby distinguish it from metastatic cancer and leukemia.

The lytic skeletal lesions of multiple myeloma are characterized by sharply defined, spheroid lesions. They have smooth borders and effaced/erased trabeculae. Unique spheroid myeloma lesions appear to be responsible for the "punched out" appearance of affected bone. The total absence of remodeling in myeloma forms a contrast to irregular preservation of trabeculae and buttressing, isolated "fronts of" cortical bone "resorption" coalescing to confluence, and the "golf-ball surface" phenomenon observed in metastatic cancer. The uniform effacement of both cortical and trabecular bone in multiple myeloma also contrasts with some cortical preservation in metastatic cancer. Leukemic lesions are more numerous than those of myeloma, but they lack the latter's "space-occupied" appearance. The relatively small holes and "fronts of resorption" of leukemia are quite different from the "space-occupied" lesions of multiple myeloma.

Uniform size is a characteristic traditionally attributed to the bone lesions of multiple myeloma. The occurrence of isolated examples of uniform size lesions in metastatic cancer and of variable size lesions in some individuals with multiple myeloma precludes unequivocal use of size in differential diagnosis. Fortunately, the newly recognized macroscopic characteristics appear to separate multiple myeloma from metastatic cancer, and also distinguish myeloma from leukemia. Am J Phys Anthropol 105:241–250, 1998.

One of the challenges of paleopathology is to establish criteria that discriminate diseases that appear to produce very similar bone lesions. That many diseases of diverse origin occasionally have similar bony manifestations creates some diagnostic uncertainty. The paleopathologist, however, has a potential advantage over the clinician. The paleopathologist can directly examine the actual effect of disease on bone. It is therefore important to establish a data base of macroscopic osseous findings in individuals with known disease.

Ragsdale (1995c) and Rothschild (1995) recently reviewed ability to recognize meta-

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static cancer. A question arose during that symposia: Can metastatic cancer be distinguished from other forms of cancer? Specifically, is it possible to distinguish lytic skeletal changes of metastatic carcinoma from those of multiple myeloma?

Metastatic cancer is well described in the literature (Brothwell, 1967; Grmek, 1975; Micozzi, 1991; Ortner, 1981; Ortner and Putschar, 1981; Rokhlin, 1965; Rothschild and Martin, 1993; Rothschild and Rothschild, 1995; Steinbock, 1975; Strouhal, 1978, 1991; Strouhal and Jungwirth, 1977; Zimmerman and Kelley, 1982). This contrasts with few descriptions of myeloma lesions and none (to our knowledge) that actually characterize the borders, other than as sharply defined or "punched-out" (radiologically) (Ortner and Putschar, 1981; Ritchie and Warren, 1932).

Previous attempts at development of criteria to distinguish multiple myeloma from metastatic cancer in defleshed skeletons have been unsuccessful (Brooks and Melbye, 1967; Cybulski and Pett, 1981; Lagier et al., 1982; Ritchie and Warren, 1932; Strouhal, 1991; Suzuki, 1981; Williams et al., 1941), although not for want of trying (Ragsdale, 1995a–c; Rothschild, 1995; Schultz, 1995; Strouhal, 1995; Winland, 1995). The sources of affected bone in those cases are often archeologic, lacking clinical verification. Examination of lytic lesions of clinically diagnosed myeloma, metastatic cancer, and leukemia allows new insights to distinguishing among them.

MATERIALS AND METHODS

The complete skeleton of a 50-year-old white male, diagnosed in life as having multiple myeloma, was examined at the National Museum of Natural History (Washington, D.C.). The skeleton (Number 787) is from the Terry collection. The latter consists of over 1,600 individuals from the St. Louis, Missouri area and is similar to the Hamman-Todd collection (Schober and Mullen, 1995), housed at the Cleveland Museum of Natural History. The Hamman-Todd collection consists of the skeletons of 2,906 individuals from the Cleveland, Ohio, area, autopsied in the early part of this century.

The pelvis, vertebrae and ribs of a second individual (Number 1789-misc) diagnosed in life as having multiple myeloma were examined at the Mutter Museum (College of Physicians of Philadelphia, Philadelphia, PA).

In addition, all individuals with diagnosed metastatic cancer (160 individuals) and leukemia (three individuals) in the Terry and Hamman-Todd collections (4,600 individuals) were examined for the presence of macroscopically detectable lytic lesions. The individuals with metastatic cancer in the Hamman-Todd collection are discussed in detail in Rothschild and Rothschild (1995). Involvement in the leukemia cases is described in detail in Rothschild et al. (1997). The diagnoses of all metastatic cancer and leukemia cases were documented in life and elicited from medical records.

Macroscopic examination of the skeleton was performed, especially noting changes in skull, long bones, vertebrae and ribs. Anterior-posterior and lateral fluoroscopy were performed on all bones, aligned in normal anatomic position, with further x-ray films obtained to selectively illustrate the pathology.

RESULTS

Observed skeletal alterations are destructive. The major changes observed are described below, from a regional perspective.

Multiple myeloma

Terry 787. Twenty-four spherical, abrupt-edged lytic lesions are visible on the external and internal diploic plates, apparently penetrating from the diploic space. The lesions are sharply defined, spheroid, and of relatively uniform diameter (0.7 cm, although rare lesions ranged in size from 1 to 14 mm). The border and internal surfaces are smooth, with no evidence of new bone formation. Exposed trabeculae appear effaced, rather than remodeled. Effaced seems an appropriate term as the boundaries are simply erased/removed, apparently by simple contact with the myeloma mass. Effaced describes an erasure, in which the adjacent zone just disappears at the very edge of the lesion. The skull lesions are predominantly basicranial (Fig. 1), sphenoid (external part, orbital roof) and temporal (anterior part on the

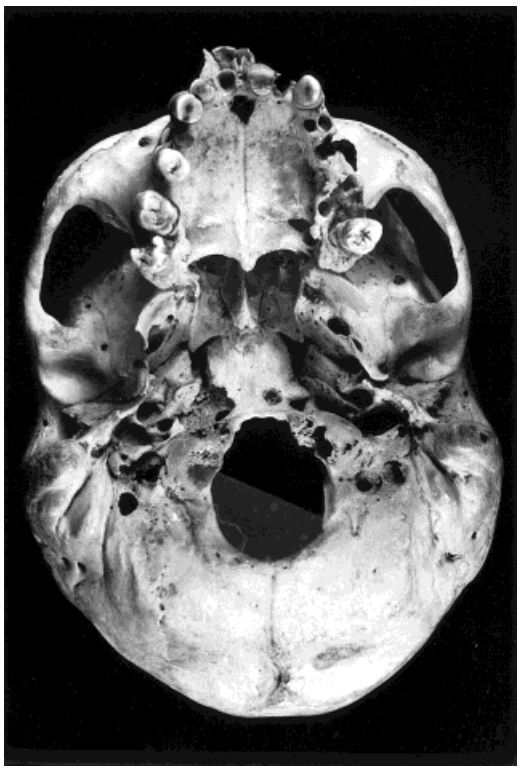

Fig. 1. Basilar view of skull (Terry 787) affected by multiple myeloma. Spherical, abrupt-edged lytic lesions, concentrated in the endochondral portion of the occipital bone. Lesions are sharply defined, spheroid, and of relatively uniform diameter. The border and internal surfaces are smooth, with no evidence of new bone formation.

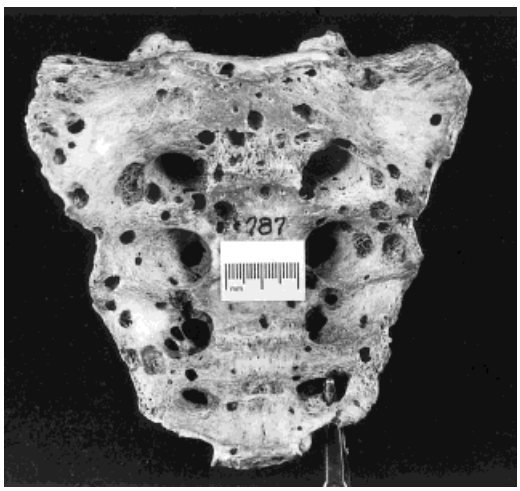

Fig. 2. Ventral aspect of sacrum (Terry 787) affected by multiple myeloma. Spherical, abrupt-edged lytic lesions. Lesions are sharply defined, spheroid, and of relatively uniform diameter. The border and internal surfaces are smooth, with no evidence of new bone formation. Exposed trabeculae appeared effaced, rather than remodeled.

angular area of the mastoid) in distribution in 787.

Post-cranial skeletal lesions vary from 1.5 to 12 mm in diameter (Figs. 2–4, 5a, 6, 7), occasionally becoming confluent (Fig. 4). Well over a hundred such lesions are present in the postcranial skeleton. They are spherical with smooth margins, identical to those observed in the skull. Osseous involvement does not spare articular surfaces (Fig. 7). Contiguous lesions penetrate subchondral bone as efficiently as the underlying trabecular bone. The spheroid shape of the mass is retained, with no regard for the density differences among the bone components affected. Macroscopically visible lesions in T-787 are distributed especially on the distal tibiae, proximal fibulae, proximal femoral metaphyses and epiphyses and clavicular metaphyses. The trochanters and articular surfaces of the tibiae, fibulae and femora are significantly affected. Ribs and sternum are diffusely affected (Fig. 6). Vertebral involvement (Fig. 4) is diffuse, equally visible in bodies, transverse and spinous processes and articular surfaces. Isolated areas of minimal periosteal reaction, below radiologic resolution, are rarely present (Fig. 3). Fewer than 1% of lesions have associated periosteal reaction. A pathologic fracture is present in the proximal fibula, bisecting a lytic lesion.

Mutter 1789-misc. Only pelvis, vertebrae and ribs are available for examination from this skeleton. More than fifty spherical, abrupt-edged lesions are visible in all bones. The lesions are sharply defined, spheroid, and quite variable in size. Lytic lesions, ranging from 1 to 13 mm, are equally represented. The border and internal surfaces are smooth, with no evidence of new bone formation. Exposed trabeculae appear effaced, rather than remodeled.

Metastatic carcinoma

Non-permeative, lytic lesions are found in six of 140 individuals with metastatic can-

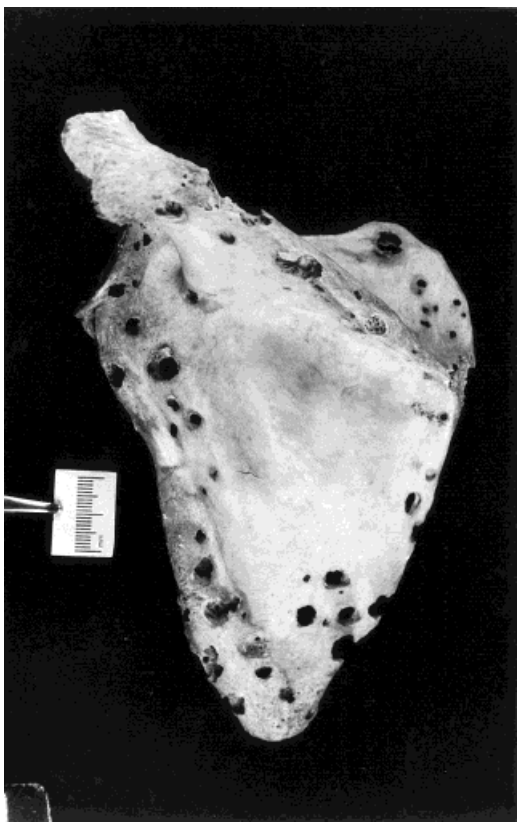

Fig. 3. Dorsal view of scapula (Terry 787) affected by multiple myeloma. Spherical, abrupt-edged lytic lesions. Lesions are sharply defined, spheroid, and of relatively uniform diameter. The border and internal surfaces are smooth, with no evidence of new bone formation. Minimal periosteal reaction is present.

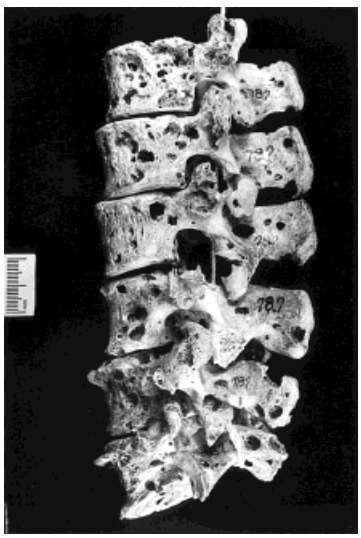

Fig. 4. Lateral view of lower thoracic and upper lumbar vertebrae (Terry 787) affected by multiple myeloma. Spherical, abrupt-edged lytic lesions involving both vertebral bodies and posterior elements. Lesions are sharply defined, spheroid, and of relatively uniform diameter. The border and internal surfaces are smooth, with no evidence of new bone formation. Only rare confluence is present.

cer. Average age in the two women and four men with purely lytic lesions is 61. Location of the initial cancer is identified in three individuals. Macroscopic lytic lesions are found in one of 32 cases of gastric cancer, one of six cases of uterine cancer, and one of three cases of prostate cancer. Lesions vary in size from 1 to 45 mm. Lesions in five individuals are quite variable in size (Figs. 5B, 8, 9). Lesions are of uniform size in one individual.

The prominent appearance is that of lytic zones. The zones appear to be the result of an expansile mass of a "space occupying or occupied appearance" (Figs. 5B, 8). Circular and geographic lesions are present. Geographic relates to irregularly shaped lesion(s) that might mimic, for example, the outline of New Jersey, rather than simply being oval or circular. This geographic shape (Fig. 9) contrasts with the spherical lesions of multiple myeloma (Figs. 1–7). Circular lesions of metastatic cancer have a nonspherical, ellipsoid component (Fig. 8), again in contrast to the spheroid lesions of multiple myeloma (Figs. 4, 6). Preservation of irregular trabeculae and rare trabecular buttressing are occasionally present at the margins of the lytic areas of metastatic cancer (Figs. 8, 9). Relative preservation of cortical bone contrasts with loss of trabecular bone (Fig. 9), at times leaving the metastatic lesion with only a residual cortical shell. The dense cortex resists metastatic invasion/destruction more than the trabecular bone, a distinction not recognized with myeloma.

"Space-occupying" lesions predominate in metatatic cancer, although two other patterns of disease are occasionally present: isolated "fronts of resorption" and a "golfball"-like surface phenomena. Isolated "fronts of resorption" are present, similar to those reported by Leisen et al. (1987) in

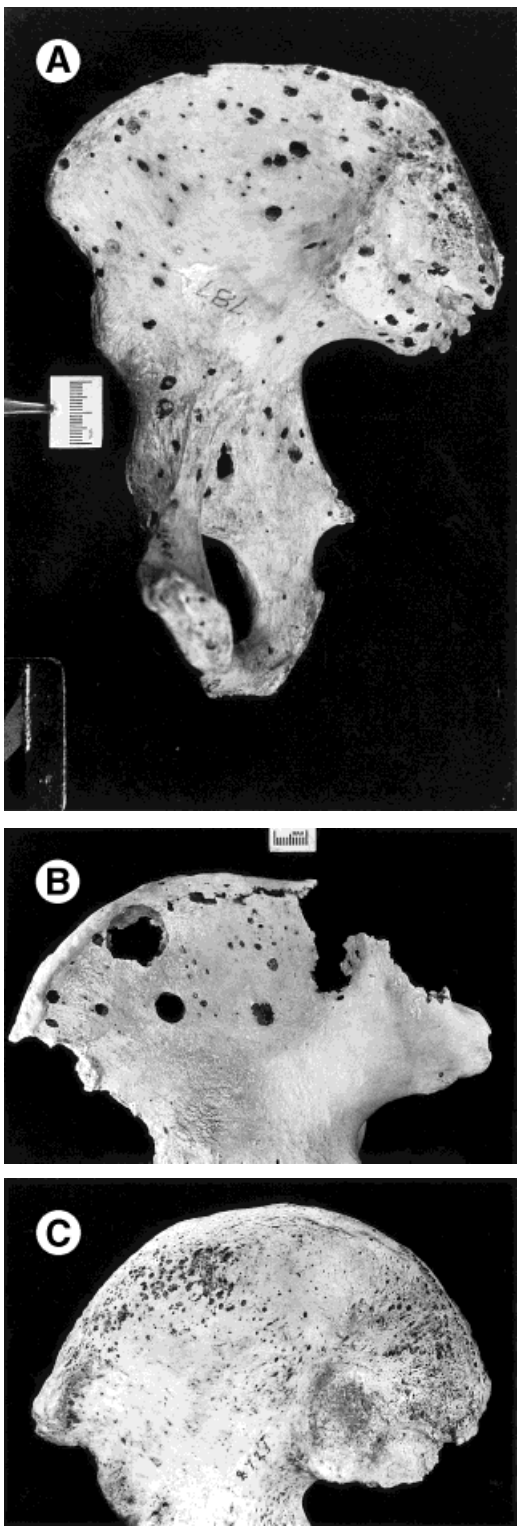

Fig. 5. Medial surface of ilia, illustrating different character of lesions in multiple myeloma, metastatic cancer and leukemia. **A:** Multiple myeloma (Terry 787). Spherical, abrupt-edged lytic lesions. Lesions are sharply defined, spheroid and of relatively uniform diameter. The border and internal surfaces are smooth, with no evidence of new bone formation. Minimal periosteal reaction is present. **B:** Metastatic cancer (HTH 788). Elliptical lytic zones, resulting from expansile masses, producing a "space-occupied" appearance. Marked size variation of individual lesion. **C:** Leukemia (HTH 2721). Large number of superficial solitary and coalescing (1 to 3 mm) pits. Holes and "fronts of resorption," with minimal periosteal reaction.

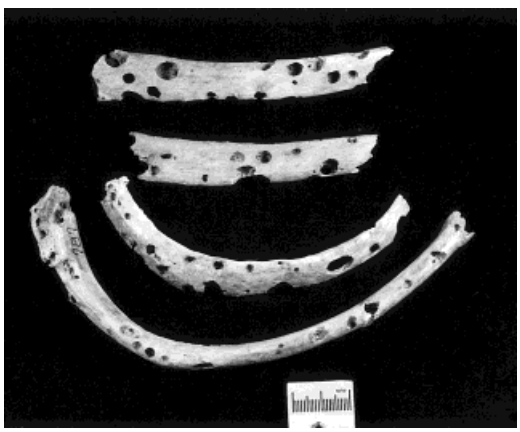

Fig. 6. Anterior and inferior views of ribs (Terry 787) affected by multiple myeloma. Spherical, abrupt-edged lytic lesions. Lesions are sharply defined, spheroid and of relatively uniform diameter. The border and internal surfaces are smooth, with no evidence of new bone formation. Exposed trabeculae appeared effaced, rather than remodeled.

marginal articular zones in rheumatoid arthritis. They differ, in that the lesions in cancer affect cortical bone and coalesce to confluence. All observed "fronts of resorption" are confluent, even in the earliest or least aggressive lesions. Most affected the skull, perforating through the diploic space. The "golf-ball"-like surface in Terry 847 is composed of a circular cranial (1.4 $\times$ 1.4 cm) defect with confluent superficial pits, creating a rugous surface (Fig. 10). Neither the confluence of individual "fronts of resorption" nor the "golf-ball" phenomena have been observed by us in any process other than metastatic cancer—in the Cobb, Dart, Grant, Hamman-Todd and Terry collections.

Lytic lesions are not as numerous in metastatic cancer, compared to multiple my-

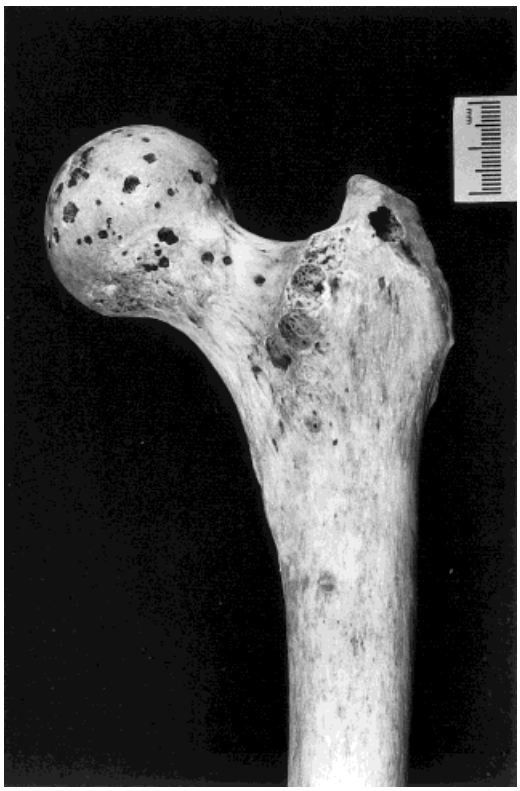

Fig. 7. Anterior view of proximal femur (Terry 787) affected by multiple myeloma. Osseous involvement does not spare articular surfaces. Contiguous lesions dissolve subchondral bone.

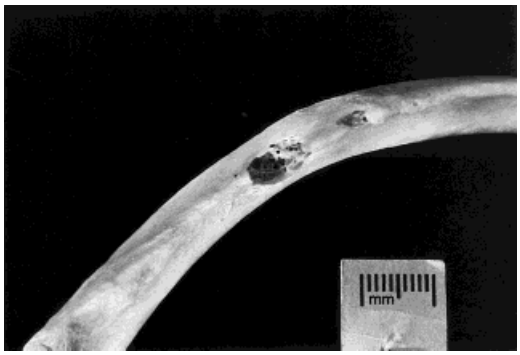

Fig. 8. Inferior view of rib (HTH 788) affected by metastatic cancer. Elliptical lytic zones, resulting from expansile masses, producing a "space-occupied" appearance. Preservation of irregular trabeculae and rare trabecular buttressing are present at the margins.

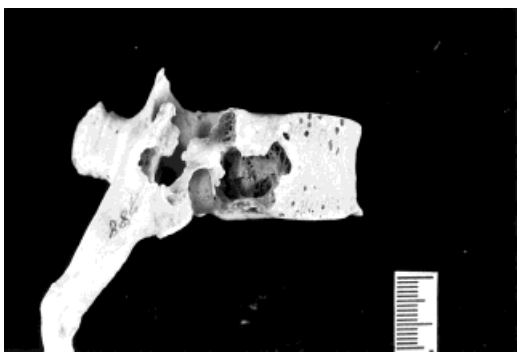

Fig. 9. Lateral view of thoracic vertebra (HTH 788) affected by metastatic cancer. Geographic lytic zones, resulting from expansile masses. Preservation of irregular trabeculae and rare trabecular buttressing are present centrally. Relative preservation of cortical bone contrasts with trabecular bone loss.

eloma. One to 43 lesions are present per bone, with scapular lesions typically most numerous. Distribution of skeletal involvement is skull 40%, vertebrae 83%, pelvis 67%, ribs 33%, femur 33%, scapula 17%, and humerus 17%.

Leukemia

One special form of cancer is leukemia. It differs in appearance from metastatic cancer. Leukemia produces massive numbers of superficial solitary and coalescing (1 to 3 mm) pits (Fig. 5C). Two components are present: Holes and "fronts of resorption." The latter are similar to those reported by Leisen et al. (1987) in marginal articular zones in rheumatoid arthritis. They differ from rheumatoid arthritis, because the lesions occurred in cortical bone, and from cancer, because coalescence to confluence is not observed in leukemia. Minimal periosteal reaction is occasionally present.

Lytic lesions are more numerous in leukemia than in multiple myeloma. They are often too numerous to count. Vertebrae, ribs, skull, clavicle, scapula, and pelvis have the most lesions in afflicted adults.

DISCUSSION

Macroscopic findings

Lytic lesions. Multiple myeloma is a variety of cancer wherein plasma cells undergo malignant transformation and growth. This neoplasm is the most common form of plasma cell dyscrasia. The term myeloma means marrow tumor, because of infiltration and

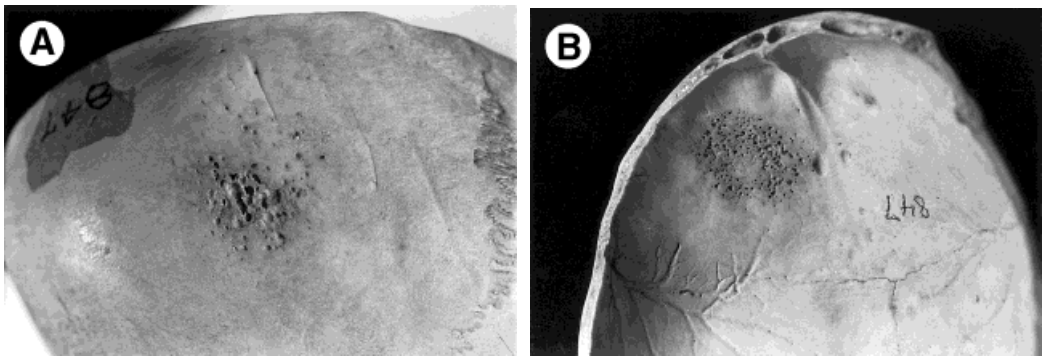

Fig. 10. Superior ectocranial (**A**) and endocranial (**B**) views of calvarium (Terry 847) affected by metastatic cancer. Localized cranial (1.4 × 1.4 cm) defect with confluent superficial pits, creating a rugous surface. Occasional coalescence (to confluence) of lesions produces a "golf-ball surface" appearance.

destruction of bone. The bone lesions have smooth borders, but no evidence of new bone formation/remodeling. Periosteal reaction is found in less than 1%. Such periosteal reaction is so minor that it cannot be seen on x-ray.

Two aspects of myeloma lesions appear especially important: Their spheroid geometry and their effaced appearance. Cortical, trabecular and even subchondral articular bone are equally penetrated/effaced by myeloma cells. Thus, the spherical geometry is retained in all lesions. When lesions enlarge sufficiently to break through cortical bone, the spheroid geometry of the lesion is visible through the circular opening.

Differential diagnosis

Shape of individual lesions. Lesions of metastatic cancer do not have an effaced appearance and are usually elliptical or geographic in shape. Circular lesions may superficially mimic myeloma, but the preservation of residual cortical shell in metastatic cancer does not occur in myeloma. Total absence of remodeling in myeloma also contrasts with irregular preservation of trabeculae and buttressing in metastatic carcinoma (Rothschild and Rothschild, 1995). Neither isolated "fronts of cortical bone resorption" coalescing to confluence nor "golf-ball surface" phenomenon are observed in multiple myeloma. They are apparently unique (at least among the two diseases) to metastatic carcinoma. Although more than 150 myeloma lesions were examined, caveat must still be expressed—this represents only two different individuals.

Multiple myeloma is also easily distinguished from leukemia (Rothschild et al., 1997). Leukemic lesions appear more numerous than those of myeloma and do not have the latter's "space-occupied" appearance. The relatively small holes and "fronts of resorption" (Fig. 5C) characteristic of leukemia are easily distinguished from the trabecular-effacing "mass" lesions of myeloma.

Size of individual lesions. Lesions of multiple myeloma are usually thought of as uniform in size, and those of metastatic cancer are more often thought of as variable in size in a given individual (Resnick and Niwayama, 1988; Rothschild and Martin, 1993). However, significant variation in size of lesions is present in one individual with myeloma and uniformity of lesion size is present in another with metastatic cancer. Size variation does not appear to be a sufficiently reliable criterion for distinguishing between the diseases.

Distribution of individual lesions. Could the distribution of lytic lesions provide another clue to diagnosis, as it does for inflammatory arthritis (Rothschild and Woods, 1991, 1992; Rothschild et al., 1990)? Metastatic cancer often produces fewer lesions, in contrast to extensive involvement in myeloma. Leukemic lesions are more plentiful than those of myeloma, in the individuals studied.

Skull, vertebral, pelvis, rib, femoral, scapular are common in all three disorders and vertebral involvement generalized in distribution. Posterior elements of vertebrae are equally affected as the vertebral body. Facet joint (articular) lesions, however, are not observed in metastatic cancer or leukemia. Sternum, tibial and fibular involvement are extensive in myeloma, while the humerus is more often affected in metastatic cancer. The skeletal distribution in leukemia is similar to that of myeloma, but with peripheral limb elements spared in the limited study group (Rothschild et al., 1997).

The evidence of distribution is not as impressive as the character of the individual lesions. As myeloma can occur as an isolated lesion (referred to as a plasmacytoma), the number of lesions cannot be considered diagnostic.

Distinguishing postmortem damage. The lesions of myeloma are so spheroid in shape and independent of hardness of affected bone that they are easily distinguished from postmortem changes which have greatest effect on less dense structures. The spheroid lesions of myeloma are also clearly distinguished from the channels of plant roots, boring insects and snails (Ascenzi and Silvestrini, 1984; Behrensmeyer, 1978; Garland, 1987; Hackett, 1981; Wells, 1967).

Lesions of myeloma are easily distinguished from puncture damage, recognizable as circular or elongated depression(s). The latter is often associated with adherent jagged-edged cortical fragments, typically oriented perpendicular to the defect (Milner and Smith, 1989; Rothschild, 1992). Postmortem damage is also readily distinguished from antemortem biologic process-related lytic lesions, if signs of bone remodeling are present. Presence of fronts of resorption in metastatic cancer and leukemia clearly rules out postmortem alteration.

Blastic lesions. One additional aspect of multiple myeloma should be mentioned, although clinically diagnosed examples have yet to be identified. Osteoblastic involvement by multiple myeloma can be so extensive as to produce an "ivory"-appearing vertebra on x-ray (Resnick and Niwayama, 1988). Osteoblastic involvement by metastatic cancer has been well recognized (de la Rua et al., 1995; Rothschild and Rothschild, 1995; Tkocz and Bierring, 1984). Availability of suitable myeloma-affected sclerotic bone will perhaps allow development of criteria to distinguish between osteosclerotic changes of myeloma and those of cancer. That, however, is beyond the scope of this study.

Assessment of archeologic reports of multiple myeloma

Suzuki (1981) and Lagier et al. (1982) express the opinion that myeloma cannot be definitively diagnosed in the archeologic record. Acknowledging that "bone proliferation or sclerotic bone changes" did not occur in myeloma, they lacked criteria to distinguish purely lytic lesions. Other attempts to diagnose myeloma cannot be validated: The character of myeloma in documented cases is different from that of cases reported from the archeologic record. Cybulski and Pett (1981) consider multiple myeloma in an individual with lytic lesions. The fourfold range of lesion size and irregular shape of some of the lesions make that diagnosis unlikely. Presence of coalescencing rib lesions with cortical expansion also has not been reported in documented myeloma. Skull x-ray does show many lytic lesions, some of which appear punched out. However, the shape of lesions is irregular and the diagnosis of myeloma must be rejected. The cases reported by Suzuki (1981), Strouhal (1991) and Brooks and Melbye (1967) have lesions of quite variable shape, as well as size. Bone expansion is also present in the case of Brooks and Melbye (1967). The diagnosis of myeloma cannot be supported. Williams et al. (1941) and Ritchie and Warren (1932) report 3–10 mm punched out lesions. X-ray reveals lytic lesions, but they are not sharply defined. The skull lesions reported by Williams et al. (1941) are flattened, not spherical. The individual is only 10 years old, a very unusual age for multiple myeloma. Ortner and Putschar (1981) describe several other reports, about which they express diagnostic reservations. We concur. They further presented potential cases from the

Smithsonian (NMNH) collections. They expressed reservation about diagnosis of myeloma even in these three cases. We concur.

Application of the criteria developed in the current study to the above cited archeologic reports identify none that could be classified as multiple myeloma. All seem compatible with a diagnosis of metastatic cancer. Actual examination of available cited cases also revealed bony alterations at variance with those reported above for in vivo-diagnosed disease. Multiple myeloma still appears elusive in the archeologic record.

Failure to recognize multiple myeloma in the archeologic record could simply represent its rarity or could implicate alterations of modern society in its pathogenesis. It should be recalled, however, that absence of evidence is not evidence of absence. Part of past diagnostic challenges may relate to semantic confusion. Intradisciplinary approaches, by their very nature, bring together individuals who often share a vocabulary. Unfortunately, that vocabulary is quite often disparate in its definitions (Buikstra and Ubelaker, 1994; Thillaud, 1994). This appears especially true in application of radiologic concepts to description of macroscopic bone lesions. There is a difference between a lytic lesion and a "punched out" lesion. The latter is very sharply defined and circular. Emphasis on punched out lesions in radiologic reports (Resnick and Niwayama, 1988) may have limited ability to recognize myeloma. It is possible that archeologic cases have previously been misclassified as metastatic carcinoma. Perhaps review of cases of "metastatic carcinoma" in the archeologic record will reveal cases of multiple myeloma.

Denouement

It is time to question the perspective that metastatic cancer and multiple myeloma cannot be distinguished. The "traditional" discriminator of lesion size variation does not allow confident diagnosis. However, spheroid-shaped, space occupying, trabeculae-effacing lesions identify multiple myeloma and distinguish it from metastatic cancer and leukemia. The spheroid lesions of multiple myeloma reflect its ability to efface adjacent structures, without consideration of their "hardness." Articular surface-sparing in metastatic cancer and leukemia also contrasts with diffuse skeletal component involvement in myeloma, which does not spare articular surfaces. Macroscopic characteristics seem to separate multiple myeloma from metastatic cancer and leukemia.

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